The signature of the serotonin system in the chronic corticosterone depression model: a study with [^{18}F]MPPF, [^{18}F]altanserin and [^{11}C]DASB.

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Introduction

Abnormalities in the serotonin system have been proposed to contribute to the pathophysiology of major depressive disorder (MDD). An interesting pathway would be the role of a dysregulated hypothalamic-pituitary-adrenal (HPA) axis, seen in patients suffering from MDD, in the disturbed serotonergic neurotransmission. The present study aimed to further explore this hypothesis, using the corticosterone (CORT) rodent depression model, combined with PET imaging. To our knowledge, this is the first preclinical study using PET to evaluate the effects of chronic CORT on the serotonin system.

Methods

The CORT depression model was induced by means of three weeks of chronic CORT administration (40 mg/kg, s.c.) to male Long-Evans rats. Next to examining the CORT-induced effects on the behavioral level, the total body weight, the plasma corticosterone levels, and non-invasive imaging was done using three highly selective PET-radiotracers. These included [^{18}F]MPPF, [^{18}F]altanserin and [^{11}C]DASB, which allowed the visualization of the serotonin 5-HT$_{1A}$ receptor, the 5-HT$_{2A}$ receptor, and the serotonin transporter, respectively.

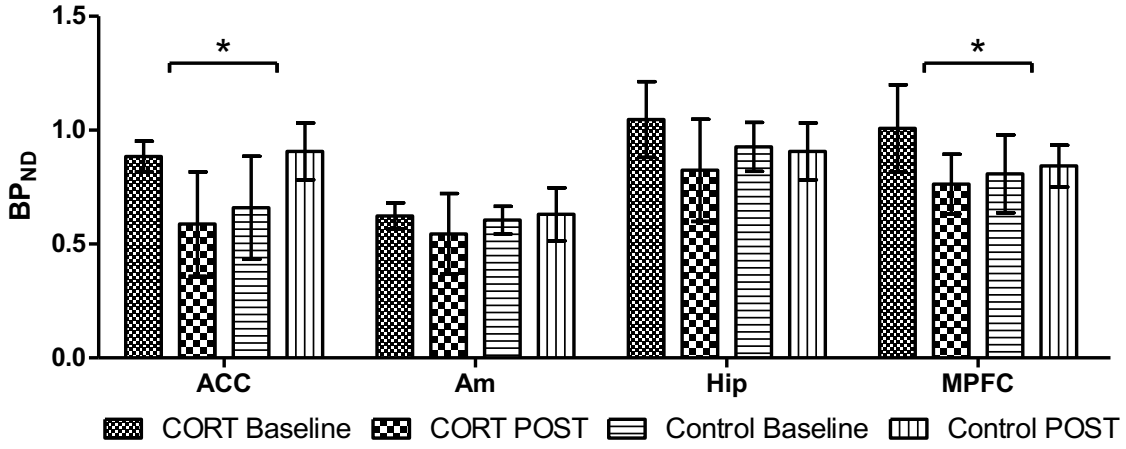
Results

The chronic CORT administration resulted in significantly lowered body weight, significantly elevated plasma corticosterone levels, and induced depression-like behavior. Compared to the control group, induction of the CORT depression model resulted in significantly decreased BP_{ND} of [^{18}F]MPPF on the 5HT$_{1A}$ receptors in the medial prefrontal cortex and anterior cingulate cortex (ACC). At the 5-HT$_{2A}$ receptor level, the [^{18}F]altanserin BP_{ND} was significantly increased in all cortical regions except for the

ACC. No significant differences in regional BP_{ND} of [^{11}C]DASB were detected. Overall, our findings at the $5HT_{1A}$ and 5-HT_{2A} receptor level are in line with previous *ex vivo* studies in rats. Furthermore, a diminished density of the 5-HT_{1A} receptors and an elevated $5HT_{2A}$ receptors has also been repeatedly observed in patients suffering from MDD.

Conclusion

The present study emphasizes the potential role of a dysregulated HPA-axis in the disturbed serotonergic neurotransmission at the $5HT_{1A}$ and $5HT_{2A}$ receptor level, seen in patient with MDD. Furthermore, these results indicate the relevance and reliability of the corticosterone depression model in the investigation of the mode of action for current and novel antidepressant therapies on the serotonin 5-HT_{1A} and 5-HT_{2A} receptors in the brain.



Effect of the CORT (n=6) and control (n=6) protocol on the regional [^{18}F]MPPF BP_{ND} values. Compared to the control group, induction of the CORT model resulted in significantly reduced (* = $p < 0.05$) BP_{ND} values in the ACC and the MPFC. ACC=anterior cingulate cortex; Am=amygdala; Hip=hippocampus; and MPFC=medial prefrontal cortex.

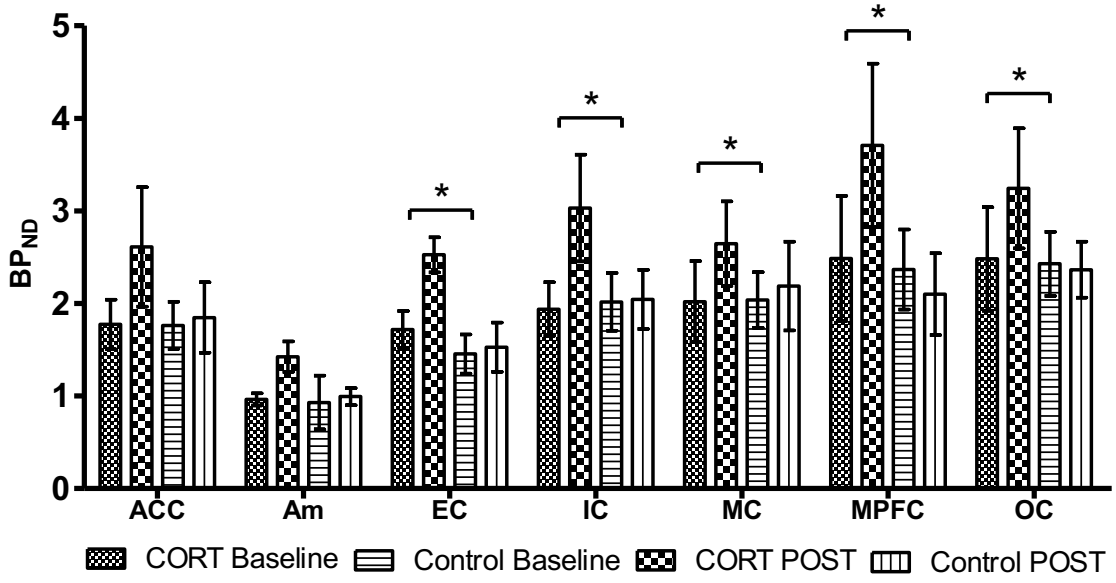


Fig 8: Effect of the CORT (n=6) and control (n=6) protocol on the regional [^{18}F]altanserin BP_{ND} values. Compared to the control group, induction of the CORT model resulted in significantly increased (* = $p < 0.05$) BP_{ND} values in the EC, IC, MC, MPFC and OC. ACC=anterior cingulate cortex; Am=amygdala; EC=entorhinal cortex; IC=insular cortex; MC=motor cortex; MPFC=medial prefrontal cortex; OC=orbitofrontal cortex.